HED DOC. NO. 014208

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

VINCLOZOLIN

(FOURTH REVIEW)

P.C. Code: 113201

FINAL REPORT

20-JUNE-2000

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: David Anderson, Toxicologist

DOCUMENT PREPARATION: Sanjivani Diwan, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

William Burnam _____

Kerry Dearfield _____

Virginia Dobozy _____

Yiannakis Ioannou _____

Nancy McCarroll _____

Timothy McMahon _____

Joycelyn Stewart _____

Clark Swentzel _____

Linda Taylor _____

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John Pletcher, Pathology _____

Lori Brunsman, Statistical Analysis _____

GUEST IN ATTENDANCE:

Michael Metzger and Whang Phang/RRB1

CONTENTS

EXECUTIVE SUMMARY

Vinclozolin (P.C. Code: 113201) was previously evaluated for carcinogenicity by the Cancer Peer Review Committee (CPRC) on August 30, 1995, April 17, 1996 and January 15, 1997. At the conclusion of the last meeting, the CPRC classified vinclozolin as "Group C-possible human carcinogen (CPRC, 1997)." CPRC recommended an extrapolation approach (Margin of Exposure or MOE) based on a NOAEL for hormone-related effects. This decision was based on the Registrant's submission of preliminary results of a re-evaluation of pathology slides from the ovary and prostate of the rat. The Committee provisionally accepted these data. Based on these data, the only tumor type with a statistically significant increase was Leydig cell tumors in male rats. Also, some members felt that the increases in prostate tumors were equivocal, but could not be dismissed.

On April 19, 2000, the Cancer Assessment Review Committee (CARC) met to discuss possible children's susceptibility to vinclozolin-induced Leydig cell tumors. The discussion of the meeting was centered around the following issues: 1) The acceptability of the Pathology Working Group's (PWG) confirmation of the lack of any compound-related ovarian and prostate tumors in the rat chronic toxicity/carcinogenicity studies; 2) Selection of a point of departure (POD) based on antiandrogenic effects seen in the prenatal/postnatal studies, perinatal study, 2-generation reproduction study and other special studies in rats (measuring changes in LH and testosterone, sperm count, and changes in reproductive organ weights and histopathology) as well as chronic toxicity/carcinogenicity studies in rats and dogs; and 3) Determination of whether the POD is sufficiently protective of infants and children from vinclozolin-induced testicular Leydig cell tumors.

The CARC accepted the PWG's report on the re-evaluation of the ovarian and prostate adenomas. Based on the review of available data, the CARC concluded that infants, children and adults would be protected from vinclozolin-induced testicular Leydig cell tumors (TLCT) through a non-linear assessment with a POD of 3 mg/kg/day and a MOE approach. (The FQPA factor and consequently the MOE necessary to protect infants and children will be determined by the FQPA Safety Factor Committee.) The CARC determined that the mode of action for vinclozolin related antiandrogenic effects in infants, children and adults is mediated via inhibition of androgen receptors. In addition, the Committee concluded that (1) Although the detailed mechanism is unknown, it has been shown that the antiandrogenicity and possibly the increased levels of LH are contributing factors to the development of Leydig cell hyperplasia (TLCH)/tumors; (2) It is unlikely that there will be a carcinogenic hazard or risk concern for infants or children exposed to vinclozolin given that the likelihood of Leydig cell tumor formation in these individuals is small. However, the potential for increased incidence of testicular Leydig cell tumors in adults resulting from infant and childhood exposure to vinclozolin cannot be ruled out; (3) Therefore, the weight of the evidence indicates that it is biologically plausible that the antiandrogenic effects of vinclozolin lead to the formation of the Leydig cell hyperplasia/tumors and that protecting against antiandrogen effects would

protect against Leydig cell hyperplasia/adenomas; (4) A NOAEL of 3 mg/kg/day for the lowest physiological antiandrogen response seen in perinatal developmental toxicity studies with a LOAEL of 6 mg/kg/day, would be protective of TLCH and TLCT. However, the risk managers should be aware of the fact that the LOAEL is very close to the NOAEL; (5) At dose levels lower than a LOAEL of 6 mg/kg/day, potential effects could not be statistically distinguished from the normal variation in androgenization of male and female rat offspring not dosed *in utero*. Therefore, given the commonality in the mode of action, a POD based anti-androgenic effect should be protective of both cancer and non-cancer effects.

I. INTRODUCTION

Vinclozolin has been evaluated by the Cancer Peer Review Committee (CPRC) previously on August 30, 1995, April 17, 1996 and January 15, 1997. At the conclusion of the last CPRC meeting, it was classified as a "Group C-possible human carcinogen" based on the increased incidence of testicular Leydig cell (i.e., interstitial testicular cells) tumors in rats supported by the increased incidence of testicular Leydig cell hyperplasia in mice (CPRC, 1997). The CPRC concluded that the currently available data appear to demonstrate an anti-androgenic activity by vinclozolin as the mode of action for testicular Leydig cell tumor formation. The CPRC recommended that for the purposes of dose-response assessment and characterization, a non-linear approach using a MOE based on a NOAEL for antiandrogenic effects should be used for quantitation of potential human cancer risk. In addition, the CPRC recommended the toxicity endpoint selected by the Toxicity Endpoint Selection Committee (HIARC, 1999) be utilized. This toxicity endpoint was based on a decrease in epididymal weight at 30 mg/kg/day seen in a 2-generation study. The dose selected for risk assessment was 4.9 mg/kg/day (NOAEL).

II. BACKGROUND INFORMATION

Vinclozolin is currently being evaluated for reregistration eligibility. As a part of this evaluation, HED was asked to determine the potential cancer risk to infants and children exposed to this pesticide. An Ad Hoc meeting was held among the scientists in HED on March 17, 2000, to discuss this issue. The participants were David Anderson, Karl Baetcke, Vicki Dellarco, William Hazel, Elizabeth Mendez, Michael Metzger, and Whang Phang. The discussion was focused on the issue of vinclozolin's anti-androgenic effect and its relationship with the induction of testicular Leydig cell tumors in rats, as well as its implications for potential risk to infants and children. A key question to address was whether this mode of action would result in testicular Leydig cell tumors in children. It was agreed that the possibility of development of testicular Leydig cell tumors later in life resulting from childhood exposure could not be dismissed, although formation of these tumors in children was unlikely. It was also agreed that if the toxicity endpoint for antiandrogenic effects, precursors to tumor and hyperplasia formation, were used for cancer risk assessment, it would be protective for tumor formation which occurred at higher dose levels than the anti-androgenic effects. The meeting participants also observed that in a perinatal rat developmental toxicity study (Gray et al., 1999), a decrease in prostate weight was seen in rats which received vinclozolin at doses as low as .6 mg/kg. The NOAEL for this effect was 3 mg/kg. After considering all the data, the meeting participants concluded that it appears to be more reasonable to base the toxicity endpoint for cancer risk assessment on the effects observed in the Gray et al. study (decrease in prostate weight at .6 mg/kg) and the dose for point of departure (POD) at 3 mg/kg. The Ad Hoc meeting also concluded that this issue should be considered by the CARC.

On April 19, 2000, the Cancer Assessment Review Committee (CARC) met to discuss the potential

cancer risk to infants and children from exposure to vinclozolin. Dr. David Anderson presented information and the issues which were the focus of the meeting (CARC, 2000a). The issues addressed in the meeting were: (1) Evaluation of the PWG report in light of the confirmation of the conclusions of the 3rd CPRC meeting on vinclozolin that there were no significant ovarian or prostate tumors from exposure to vinclozolin (CARC, 2000b); (2) Reassessment of the POD for a non-linear risk assessment of testicular Leydig cell adenomas from exposure to vinclozolin; and (3) The determination of whether the selected point of departure is sufficiently protective of infants and children from vinclozolin-induced testicular Leydig cell tumors.

III. EVALUATION OF THE PATHOLOGY WORKING GROUP REPORT (PWG)

The PWG (1997) evaluated the ovaries and prostates from two 24-month studies in Wistar rats dosed with vinclozolin. The PWG concluded that female rats dosed for 24 months with vinclozolin developed ovarian stromal hyperplasia only. Ovarian stromal hyperplasia is a common age-associated lesion, however, there was a nominal dose-related increase in severity of the hyperplasia. No statistically significant increased incidence of ovarian adenomas or other ovarian neoplasms was noted.

The PWG concluded that in male rats dosed over 24-months, there was an increased incidence of atypical hyperplasia of the glandular epithelium of the prostate. However, there were no statistically significant increases in the incidences of prostatic adenomas or other prostate neoplasms.

The data in this report show similar lesions to previous reports, but show fewer ovarian adenomas and prostate adenomas than in the original report reviewed for the 3rd CPRC report (HED Doc. 014143). In fact, when the criteria of Boshland (1996) were used, there was no dose response relationship seen in either the ovarian adenomas or the prostate adenomas. The CARC accepted the PWG's evaluation.

IV. EVALUATION OF ANTIANDROGENIC EFFECTS TO DETERMINE THE POINT OF DEPARTURE

A) Antiandrogenic Effects

The principal toxic effects induced by vinclozolin are related to its antiandrogenic activity and its ability to act as a competitive antagonist at the androgen receptor. There is evidence that vinclozolin binds fairly weakly to the androgen receptor but that two vinclozolin metabolites occurring in mammals, plants, and soil are responsible for much of the antiandrogenic activity attributable to vinclozolin. Some of the more

relevant information related to antiandrogenic activity of vinclozolin is summarized below.[1] For a more thorough discussion of these effects, refer to the following sources: Gray, et. al. (1999); Hellwig (1989); "2nd report of the Hazard Identification Assessment Review Committee" (HIARC, 1999) and "Developmental and Reproductive Toxicity Assessment Review Committee's report on Vinclozolin" (DRARC, 1998).

Pre-Natal Developmental Studies

In a rat developmental study (Gray et al., 1999), a variety of antiandrogenic effects were reported including decreases in prostate weight (LOAEL = 6 mg/kg/day) and increased nipple development and decreased ano-genital distance in male offspring (LOAEL = 12 mg/kg/day)[2]. Other related effects seen in male offspring included decreased seminal vesicle weights, an increased incidence of vaginal pouches, increased numbers of nipples and hypospadias, decreased ejaculated sperm counts, decreased fertility, decreased caudal epididymal weight, and an increased incidence of ectopic testes. Table 1 summarizes the results of this study.

The results of this study were used to establish endpoints for acute dietary and short-/intermediate-term dermal risk assessments. It is also the study from which the proposed new POD for cancer risk assessment was chosen (NOAEL = 3 mg/kg/day, decreased ventral prostate weight seen at LOAEL = 6 mg/kg/day)

Similarly, antiandrogenic effects were seen in Wistar and Long-Evans rats in a study conducted by BASF (Hellwig, 1997a & b). Developmental effects observed in these studies included significant increases in areolas/nipple anlagen in both strains (LOAEL = 12 mg/kg/day) and decreased ano-genital distance (LOAEL = 200 mg/kg/day). A related effect observed in other studies was ambiguous genitalia in males.

Post-Natal Developmental Study

In a post-natal study using Long Evans hooded rats (Gray et Al., 1999; HIARC, 1999), a delay in puberty (age at preputial separation) was found to be statistically significant ($p<0.05$) in male offspring at doses of 15 mg/kg/day when compared to controls. This finding was supported by significant decreases in caudal

[1] It should be noted that there is a normal variation in the degree of androgenization of individual fetuses during gestation, i.e., the androgen dependent ano-genital distance in a male fetus appears to be dependant, among other factors, on whether it is positioned between 2 male fetuses, 1 male and 1 female fetus, or between 2 female fetuses during gestation in untreated rats and mice.

[2] This high LOAEL was due to dose spacing. The statistical evaluation of a study by Gray supported a LOAEL for decreased ano-genital distance of 12 mg/kg/day in perinatal studies.

and paired epididymal weights at doses above 15 mg/kg/day. The slightly delayed puberty probably resulted from androgen deprivation from weaning to about day 40, during growth and development. Therefore, if exposed, vinclozolin may result in a delay in sexual maturation in children. This endpoint was used in the short and intermediate term risk assessments for infants' and children's subpopulations (NOAEL = 5 mg/kg/day).

Table 1: Summary of effects of vinclozolin (administered GD 14 to PND 3) on body and organ weights and other parameters measured in LE male rat offspring about 12 months of age. Information and data are extracted from Gray et al. (1999).

Table 1: Summary of Antiandrogenic Effects of Vinclozolin

Dose levels (mg/kg/day)	0	3.125	6.25	12.5	25	50	100
Body wt (g), data±SE (#litters/#males)	709±38 (9/30)	681±20 (7/37)	691±17 (8/39)	726±6 (7/46)	695±5 (4/18)	716±36 (3/6)	644±32 (2/2)
Seminal vesicle wt (mg) [b] (#litters/#males)	1945±147 (9/27)	1883±147 (7/36)	1747±102 (8/37)	1800±100 (7/45)	1744±134 (4/18)	1859±126 (3/5)	657±142 [c] (2/2)
Ventral prostate wt. (mg) [b] (#litters/#males)	**564±57 (9/27)**	**499±50 (7/36)**	***415±40 (8/37)**	**439±31 (7/45)**	****382±27 (4/18)**	****305±33 (3/5)**	****69±47 [c] (2/2)**
Testes wt (g) (#litters/#males)	3.71±0.09 (9/24)	3.63±0.06 (7/19)	3.55±0.12 (8/23)	3.69±0.15 (7/18)	3.82±0.14 (4/13)	3.55±0.12 (3/6)	3.48±0.14 (2/2)
Adrenal wt (mg) (#litters/#males)	46±3 (5/13)	50±6 (3/12)	49±1 3/13	43±5 (2/10)	43±0.2 (2/6)	45±3 (3/6)	60±19 (2/2)
Cauda epididymides (mg) (#litters/#males)	316±9 (9/24)	311±10 (7/19)	303±9 (8/23)	323±7 (7/19)	304±16 (4/13)	287±21 (3/6)	**213±82 (2/2)
Cauda epididymal sperm (x 10^6) (#litters/#males)	152±9 (5/12)	134±13 (3/12)	133±16 (3/13)	152±10 (2/10)	153±20 (2/6)	148±25 (3/6)	*67±67 (2/2)
Testis spermatids (x 10^6) (#litters/#males)	218±11 (5/13)	213±4 (3/12)	206±4 (3/13)	219± (2/10)	223±22 (2/9)	191±28 (3/6)	175±7.5 (2/2)
Low ejaculated sperm count (<10^6)	0/14	0/13	1/13	0/10	0/6	3/6	3/3
Ejaculated sperm (x 10^8)	1.84±0.12 (5/13)	1.87±0.17 (3/12)	1.82±0.15 (3/12)	2.03±0.1 (2/10)	1.93±0.01 (2/6)	**0.18±0.16 (3/6)	**0 (3/3)
Fertility	100%	100%	92%	100%	100%	*50%	**0%
Percentage with hypospadia (#litters examined/#males examined)	0 (19/77)	0 (16/96)	0 19/117)	0 (12/84)	0 (11/56)	45±16 (3/11)	100 (2/7)
Percentage with nipples (#litters examined/#males examined)	**0 (19/77)**	**1.0±1.0 (16/96)**	**2.6±1.4 (19/117)**	**3.6±2.0 (12/84)**	**5.4±3.0 (11/56)**	****91.0±9.0 (3/7)**	****100 (2/7**
(# pups with nipples)/(#pups examined); [minimum # litters affected] [e]	**0/200-300 [d] [0]**	**1/96 [1]**	**3/117 [2 or 3]**	**3/84 [2 or 3]**	**3/56 [2 or 3]**	**6/7? [3]**	**7/7 [2]**
Serum testosterone (ng/ml) (litters examined/pups examined)	1.85±0.55 (5/13)	1.35±0.14 (3/12)	1.70±0.37 (3/13)	1.94±0.2 (2/10)	1.89±0.05 (2/6)	1.39±0.53 (3/6)	1.52±0.41 (2/2)
Percentage ectopic testes (litters examined/pups examined)	0 (19/77)	0 (16/96)	0 (19/117)	0 (12/84)	0 (11/56)	0 (3/11)	20 (2/10)

*, ** = p # 0.05 or #0.01. [a] = Data were analyzed using litter means. [b] = Seminal vesicle and prostate weights were not measured in those males that displayed gross inflammation and/or discoloration of the sex accessory tissue. [c] = Tissue were inflamed but included for comparison [d] =

2-Generation Reproduction Study

A 2-generation reproduction study in rats was submitted by BASF (Hellwig, 1997 a& b). For a detailed discussion of this study refer to the report of the DRARC (1998). Results pertinent to this discussion are summarized in Table 2 below.

Table 2. Vinclozolin: 2-Generation Reproductive Study in Rats (Hellwig, 1997 a & b)

Histological finding	Control	4.9 mg/kg/day	30 mg/kg/day	96 mg/kg/day	290 mg/kg/day
24 animals per group were used in each generation, except where noted					
P_0 males					
Leydig cell hyperplasia	0	1	0	10	16
Leydig cell adenomas	0	0	0	0	0
F_1 males					
Leydig cell hyperplasia	2	0	7	17	24 (n=29)
Leydig cell adenomas	1	0	0	0	4
F_1X males					
Leydig cell hyperplasia	0	0	0	19	38 (n=49)
Leydig cell adenomas	0	0	0	0	0
F_2Y males					
Leydig cell hyperplasia	0	0	1	no offspring	no offspring
Leydig cell adenomas	0	0	0	no offspring	no offspring
F_2Z					
Leydig cell hyperplasia	2	0	2	no offspring	no offspring
Leydig cell adenomas	0	0	0	no offspring	no offspring

** $p<0.01$

The high dose F_1 males had a significantly increased ($p < 0.01$) trend for testicular Leydig cell adenomas. However, no significant increase was noted in a pair-wise comparison of the high-dose group with the control. Testicular Leydig cell hyperplasia was seen at doses of 30 mg/kg/day and above. The incidence of Leydig cell

hyperplasia was increased in the F_1 generation relative to the parental animals. This increased incidence was possibly due to the increased duration of dosing of the F_1 generation relative to the P_0 generation, the F_1 animals being dosed up to 28-34 weeks, including *in utero* exposure and dosing prior to sexual maturity. It is a significant finding that an increase in the incidence of the same type of lesion was seen from dosing rats *in utero* through sexual maturity into adulthood and from dosing young adult rats for 22-28 weeks (P_0 parental generation). This suggests that Leydig cell hyperplasia is a common effect with vinclozolin resulting from dosing the animals both as adults and from dosing the animals prior to sexual maturity.

Chronic Dog Study

In a 1-year chronic dog study, increased relative testes weights and prostate atrophy were observed at the LOAEL = 4.8 mg/kg/day (NOAEL = 2.4 mg/kg/day).

Endpoints Considered

Table 3 summarizes the antiandrogenic effects of vinclozolin seen in various studies (HIARC, 1999; DRARC, 1998, CPRC, 1997).

Table 3. Endpoints considered during deliberations of the CARC. The table includes relevant data from the available studies.

Study	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Findings
Pre/postnatal/Rat	3 6 4.9 25	6 12 30 50	Decreased prostate weight Ano-genital distance decreased, areolas/nipples increased Epididymal weight decrease, testicular Leydig cell hyperplasia Seminal vesicle weight decrease
2-Generation reproduction/Rat	4.9	30	Epididymal weight decrease, testicular Leydig cell hyperplasia
Other/Rat	5 5 25 50	15 15 50 100	Delayed puberty LH increase Hypospadias, ejaculated sperm decrement Testosterone increase
Chronic dog	2.4	4.8	Testes weight increase, prostate atrophy
Chronic rat	23 (500 ppm) 1.2 (25 ppm)	71 (1500 ppm) 2.4 (50 ppm)	Reduced prostate size (at gross/necropsy) Foam cell aggregates lenticular degeneration in males and interstitial cell lipidosis in females based on MRID# 43254703.
Cancer/Rat	2.3 (50 ppm)	23 (500 ppm)	Testicular Leydig cell adenoma increase

B) Mode of Action for Testicular Leydig Cell Hyperplasia and Tumor Formation

The Second Carcinogenicity Peer Review for Vinclozolin (CPRC, 1996) concluded that the anti-androgenic mode of action for the testicular Leydig cell tumors in rodents appears to have been

demonstrated. For details, see the 2nd & 3rd CPRC (1996 and 1997).

In general, it was concluded that vinclozolin and some of its metabolites competitively bind to androgen receptors thus reducing androgen binding. This results in an increased release of luteinizing hormone (LH) which stimulates testosterone production in testicular Leydig cells and Leydig cell hyperplasia by an unknown mechanism. Although the detailed mechanism is unknown, it has been shown that the anti-androgenicity and possibly the increased levels of LH are contributing factors to the development of Leydig cell hyperplasia/tumors. Therefore, the weight of the evidence indicates that it is biologically plausible that the anti-androgenic effects of vinclozolin lead to the formation of the Leydig cell hyperplasia/tumors and that protecting against anti-androgen effects would protect against Leydig cell hyperplasia/adenomas.

V. RECONSIDERATION OF THE POD FOR NON-LINEAR CANCER RISK ASSESSMENT

In order to assure adequate protection of all susceptible adult subpopulations considering potential exposures throughout their lifetimes, CARC recommended that the cancer risk assessment should be performed utilizing the most sensitive endpoint related to vinclozolin's antiandrogenic effects. This endpoint is identical to that used for the short and intermediate term noncancer risk assessment (i.e., decreased ventral prostate weights). This effect was seen at 6 mg/kg/day. Previously, a NOAEL of 4.9 mg/kg/day was used as a POD for threshold carcinogenic dose-response assessment. The endpoint was based on decreased epididymal weight seen at 30 mg/kg/day in a 2-generation rat reproduction study. While this endpoint may be protective for some adult populations and exposure durations based on the results of the 2-generation reproduction study, there is concern that it may not be protective of all subpopulations and longer exposure durations because antiandrogenic effects were seen at lower dose levels in the developmental rat studies. The CARC, therefore, recommended that a POD of 4.9 mg/kg/day be replaced with the 3 mg/kg/day given that this NOAEL is protective for all antiandrogenic effects which could lead to Leydig cell tumor formation, and is, therefore, protective of all population and for all exposure durations.

VI. ASSESSMENT OF CHILDREN'S SUSCEPTIBILITY

The toxicity profile for vinclozolin clearly indicates that the toxic effects of most concern to infants and children are the reproductive and developmental effects related to the chemical's antiandrogenic properties. Two of these effects, decreased prostate weight and delayed puberty, are selected as endpoints for noncancer human health risk assessments.

The cancer end point of concern related to vinclozolin exposure is the formation of testicular Leydig cell tumors. As described above, it has been concluded that it is biologically plausible that Leydig cell tumors result from the pesticide's antiandrogenic properties. Because the optimal hormonal milieu for formation

of these tumors occurs predominantly in adult animals following chronic treatment with vinclozolin, it is unlikely that there will be serious concern for formation of these tumors during childhood. Although formation of these tumors in children is unlikely, the young adults males do develop testicular cancer. An increased incidence of testicular Leydig cell hyperplasia in adult animals may result from dosing of the animals prior to sexual maturity (including *in utero* exposures) as suggested by the results of the 2-generation reproduction study discussed above. It is a significant finding that the same types of lesions are formed in adult males from dosing of both adult and immature animals.

Data on human cancer indicate that Leydig cell tumors are uncommon in adult males. Approximately 1% of all cancers in men are of testicular origin, and only 1% of that are Leydig cell tumors (i.e., 0.01% of all cancer in men) (Contran et al., 1994; Gilliland and Key, 1995). Approximately 10-15% of Leydig cell tumors in men can be malignant (Grem et al., 1986). Leydig cell tumors are extremely rare in children, and when they do occur they are exclusively benign (Kaplan et al., 1986). According to a 1994 paper by Grapin et al. (1994), the incidence of testicular tumors in children is approximately 1 in 100,000 male children. Furthermore, a 1996 paper by Jimenez et al. (1996) states that "in patients under 14 years, the incidence of testicular or paratesticular tumors is 0.5 - 2/100,000" with Leydig cell tumors accounting for approximately 7% of those tumors. Thus, the occurrence of Leydig cell tumors in the US population does not indicate an increased susceptibility of children to development of this tumor type. Nevertheless, the possibility of increased incidence of testicular Leydig cell tumors in adults resulting from childhood exposure to vinclozolin cannot be ruled out.

VII. CARC'S CONCLUSIONS

The CARC determined that:

1) The PWG's evaluation of ovarian and prostate tumors in a 24-month study with Wistar rats was acceptable;

2) The NOAEL of 3 mg/kg/day should replace the NOAEL of 4.9 mg/kg/day as the POD to be used for a non-linear (MOE) approach for cancer risk assessment;

3) The MOE approach using a POD of 3 mg/kg/day for the most sensitive antiandrogenic effect should be protective of all population subgroups and durations of exposure, including exposures to infants and children, for cancer concerns;

4) It is unlikely that there will be a carcinogenic hazard or risk concern for infants or children exposed to vinclozolin given that the likelihood of Leydig cell tumor formation in these individuals is small. However, the potential for increased incidence of testicular Leydig cell tumors in adults resulting from infant and children exposure to vinclozolin cannot be ruled out;

5) The formation of other types of tumors in infants and children from vinclozolin exposure is unlikely. Although other types of tumors were reported in the available cancer studies (i.e., ovarian and prostate tumors), the CARC concluded that the increases in the occurrence of these tumors were not biologically significant; and

5) It should be emphasized that testicular Leydig cell tumorigenesis is the cancer effect of concern in the animal bioassays. However, the reproductive consequences that may also result from vinclozolin's antiandrogenic mode of action are of equal concern. Therefore, given the commonality in the mode of action, a POD based on antiandrogenic effects should be protective of both cancer and noncancer health consequences. However, the risk managers should be aware of the closeness of the NOAEL and the LOAEL for antiandrogenic effects of vinclozolin in animals.

VIII. BIBLIOGRAPHY

Anderson, D. G. (2000). ***Vinclozolin***: pathology Working Group (PWG) report on ovarian and prostate tumors in a chronic toxicity and oncogenicity study in rats. Memorandum by David G. Anderson, Reregistration Branch 2, Health Effects Division to Susan Lewin/Deanna Scher, Reregistration Branch 1, SRRD dated April 18, 2000. HED Doc. # 014143.

CARC (1996). Carcinogenicity Peer Review of ***Vinclozolin (2nd).*** A memorandum from David Anderson, Toxicology Branch I and Esther Rinde, Science Analysis Branch, Health Effects Division (7509C) to Connie Welch, Registration Division (7505C) and Bruce Sidwell, Special Review and Reregistration Division through Stephanie Irene, Health Effects Division (7509C), Office of Pesticide Programs.

CARC (1997). Carcinogenicity Peer Review of ***Vinclozolin (3rd).*** A memorandum from Edwin R. Budd and Esther Rinde, Health Effects Division to Connie Welch, Registration Division (7505C) and Bruce Sidwell, Special Review and Reregistration Division through Stephanie Irene, Health Effects Division (7509C), Office of Pesticide Programs, dated April 3, 1997. HED Doc. 012639

CARC (2000a). ***Vinclozolin:*** Cancer Assessment Review Committee (CARC) Supplemental Meeting: Proposed Changes in the Endpoint for Cancer Risk Assessment Including the Issues of Infants and Children. A memorandum from Michael S. Metzger, RRB1 and David Anderson, RRB2, Health Effects Division to William Burnam, SAB, Health Effects Division, Office of Pesticide Programs, dated April 4, 2000.

CARC (2000b). ***Vinclozolin***: Assessment of new information relevant to carcinogenic potential. A memorandum from John M. Pletcher, Consulting Pathologist, SAIC to Sanjivani Diwan, Executive Secretary, Cancer Assessment Review Committee, Health Effects Division (7509C), Office of Pesticide Programs, dated 13 April, 2000.

Contran RS, Kumar V, Robbins SL, and Schoen FJ. (1994). Male genital system, in Robbins Pathologic Basis of Disease 5th Edition. Contran RS, Kumar V, and Robbins SL. EDs., WB Saunders, Philadelphia, 1015-1022.

DRARC (1998). Reproductive and Developmental Toxicity Peer Review of Vinclozolin. A memorandum from Kit Farwell, RRB1 to Clark Swentzel, Chairman, HIARC through David Anderson, Chairman, DRARC, Health Effects Division (7509C), Office of Pesticide Programs, dated April 7, 1998. HED Doc. 012562 .

Gilliland FD and Key CR. (1995). Male genital cancers. Cancer 75 (suppl. 1), 295-315.

Gray LE, Jr., Ostby J., Monosson E., and Kelce WR. (1999). Environmental antiandrogens: low doses of the fungicide vinclozolin alter sexual differentiation of the male rats. Toxicology and Industrial Health *15*: 48-64 (portions of the data used were also from the 1996 SAP presentation).

Grem JL, Ronins HI, Wilson KS, Gilchrist K and Trump DL. (1986). Metastatic Leydig cell tumor of the testis. Report of three cases and review of the literature. Cancer Res. 58:2116-2119.

Grapin C, Boyer C, and Bruner M. (1994). "Tumor of the Testes in Children." J. Urol. 100(12): 8-16.

HIARC (1999). Toxicology Endpoint Selection Document. 2nd Report of Hazard Identification Review Committee, dated December 8, 1999, HED Doc. # 013919.

Hellwig, J. (1997a). Pre-/postnatal toxicity study in Wistar rats after oral administration (gavage). Reg No. 83-258, Dept of Toxicology, BASF Akiengesellschaft, FRG. 9/1/97 . Unpublished, MRID 44395701.

Hellwig, J. (1997b). Pre-/postnatal toxicity study in Long Evans rats after oral administration (gavage). Reg No. 83-258, Dept of Toxicology, BASF Akiengesellschaft, FRG. 9/1/97 . Unpublished, MRID 44395702.

Jimenez, IM, Gomez, FA, Aransay, BA. et. al. (1996). Testicular tumors in childhood. Review of cases in the course of 13 years." Cir. Pediatr. 9 (1): 13-16.

Kaplan GW, Cromie WJ, Kelalis PP Silber I and Tank ES, 1986. Gonadal stromal tumors: A report of the prepubertal testicular tumor registry. J. Urol. 136:300-302.

Pathology Working Group Report (1997). Vinclozolin, Reg. No. 83 258 ; 24-Month Chronic Toxicity (BASF Project No. 71S0375/88026) and Carcinogenicity (Project No. 71S375/88105) Studies in Wistar Rats. Report prepared by PathCo Inc., August 28, 1997, 372 pages plus 1a & 1b. BASF Reg. Doc. # 97/11184. (MRID# 44430301) Case 819455, Rereg. case# 2740.